Cytotoxic pathways of enteroviral myocardial infection

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This editorial refers to ‘Enterovirus-related activation of the cardiomyocyte mitochondrial apoptotic pathway in patients with acute myocarditis’¹, by L. Venteo et al. on page 728

Knowledge of a disease pathway represents in general a prerequisite for a more precise definition of disease prognosis as well as a valuable hint to provide the patient with the most appropriate therapeutic regimen. During an acute myocarditis caused by enterovirus (EV) several mechanisms of myocardocyte damage can actually be recognized including (Figure 1): (α) the induction of an inflammatory reaction to the infectious agent; (β) the release of destructive proteases from the host; and (γ) the activation of intracellular apoptotic pathways. In particular, EV myocardial inflammation (α), even through stimulation of Toll-like receptors, is always associated with biological events such as release of cytokines, complement (mainly components C8–C9) and T lymphocyte-bound perforins that jeopardize cell structure and function as well as the integrity of the interstitial compartment. Additionally, in a limited cohort of patients with a human leucocyte antigen (HLA) system capable of presenting on the cardiomyocyte membrane a segregated autoantigen (such as myosin) or newly formed virus-shared antigens (antigenic mimicry), autoimmune process can be activated leading to a chronic myocardial inflammation and progressive heart failure.

Protease 2A (β) is a well known product of Coxsackievirus B which is able to cleave the cytoskeleton protein dystrophin and disconnect myofilaments from the sarcolemma membrane, inducing a progressive degradation and loss of contractile elements.⁴

The study of Venteo et al.⁵ focuses on mitochondrial apoptotic pathways (γ) activated in cardiomyocytes during an acute EV myocarditis compared with healthy controls. The authors reveal that in patients with EV-associated acute myocarditis, cardiac VP1 expression appeared to be high. Likewise in patients with EV-associated acute myocarditis, apoptotic cardiomyocytes were detected in a significantly higher number than in those with EV-negative myocarditis or in controls, indicating a direct cytotoxic effect of the viral infection leading to cardiac cell death through apoptosis. Similar results were achieved by investigating the cytosolic/mitochondrial cytochrome c concentration and level of active caspase-9 which was significantly decreased in EV compared with non-EV-related myocarditis patients. On the basis of this evidence, the authors conclude that EV cardiac replication activity measured by expression of VP1 EV protein within the myocardium induces a differential modulation of the cardiomyocyte mitochondrial apoptotic pathway in patients with active myocarditis compared with non-viral myocarditis, which can be in part responsible for the progression from EV-related myocarditis to end-stage dilated cardiomyopathy (DCM). The observation in EV-infected myocardial tissue of a compensatory upregulation of the anti-apoptotic Bax with an increase of the Bax/Bcl2 mRNA ratio seems to confirm the authors’ statements.

Venteo’s work has the merit of recognizing a viral-mediated activation of mitochondrial apoptotic pathway in patients with EV myocardial infection. Quantification of its impact on loss of cardiac function particularly in comparison with inflammation (α) and the myofibrinolysis (β) pathway is, however, not available. In addition, its role in the progression of acute EV myocarditis to end-stage EV DCM is not conclusive. Quantitative evaluation of a specific role for the α, β, and γ pathways respectively, on the impairment of cardiac function could be theoretically obtained by studying sequential endomyocardial biopsies of patients with acute EV myocardial infection having a different outcome. Nevertheless, Venteo’s study still has a remarkable investigational interest and expands the possible targets of therapeutic interventions. In particular, acute EV myocarditis can be a life-threatening condition where there is actually a common agreement only for pharmacological [carvedilol, angiotensin-converting enzyme (ACE) inhibitors, diuretics, digoxis, vasodilators] and mechanical (left ventricular assist device) supportive therapy. High dose immunoglobulins (1 g/kg of body weight) are specifically recommended in children and immune-depressed patients with active viral replication,⁶ while immunoadsorption therapy has not yet produced conclusive results.⁷ Antiviral therapy targeting the Coxsackievirus–adenovirus

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receptor is still experimental.\(^8\) Administration of antiviral drugs has not yet provided encouraging results, and finally use of β-interferon seems to be contraindicated since in an acute viral myocarditis it could enhance myocardial inflammation.\(^9\) In this context, the report by Vénteo et al. raises the possibility that inhibition of cell apoptosis may provide a novel target for treatment directed against acute and fulminant EV myocarditis. Indeed, recently, it has been demonstrated that drotrecogin alpha, which is a treatment in sepsis-induced multiple organ failure, can induce a significant decrease of both the Bax/Bcl-2 and Bax/Bcl-xl ratios.\(^10\) This suggests the potential utility of this new drug in EV-related myocarditis patients particularly in those showing remarkable compromise of left ventricular function. An alternative option could be represented by the use of pan-caspase inhibitors Z-VAD-FMK or Q-VD-OPH that could prevent the activation of caspase-8 and caspase-9 during acute myocardial infection by EV.\(^11\) For subacute or chronic EV-induced myocardial inflammation, additional therapeutic means can be considered such as immunosuppression in patients with virus-negative inflammatory cardiomyopathy, where a positive response in terms of recovery of cardiac function can be obtained in >80% of cases,\(^12,13\) and use of growth factors such as growth hormone in patients with extensive myocyte vacuolization because of myofibrillolysis as an attempt to stimulate the re-synthesis of contractile elements.\(^14\)

In conclusion, in their work Vénteo et al. recognize a viral-mediated activation of mitochondrial apoptotic pathway in patients with acute EV myocardial infection. They suggest new therapeutic targets to cure EV-associated acute heart failure. Further studies are needed to confirm the translational impact of their observation.

**Conflict of interest:** none declared.

**References**


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**CARDIOVASCULAR FLASHLIGHT**

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**Spontaneous closure of a coronary fistula due to cardiac allograft vasculopathy**

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A 27-year-old patient underwent cardiac transplantation in 2002 due to dilated cardiomyopathy. The transplanted heart had a large congenital coronary fistula (arrow) from the ramus circumflexus (RCX) to the left atrium (LA), which was regularly surveyed during follow-up by echocardiography (Panel A) and by coronary angiography (Panel B). A percutaneous closure of the fistula was discussed but not performed due to lack of symptoms and excellent clinical status.

The most recent routine coronary angiography surprisingly revealed a spontaneous closure of the fistula (Panel D). The previously enlarged RCX had a normal calibre now, and conversely, the LAD calibre had increased relative to that of the RCX. Intravascular ultrasound of the LAD showed an impressive intimal hyperplasia (Panel C: 1, IVUS catheter; 2, lumen of the LAD; 3, intimal hyperplasia) due to cardiac allograft vasculopathy (CAV).

Cardiac allograft vasculopathy is characterized by diffuse intimal hyperplasia and is the main cause of graft loss and death in heart transplant recipients surviving >1 year. Coronary fistulas are very rare malformations and spontaneous closure of small fistulas has been reported even less often. In our patient, the fistula was large and we believe that spontaneous closure was due to considerable intimal hyperplasia.

Until better than the actual means against CAV will be found, a conservative approach in the treatment of coronary fistulas is probably warranted in patients after heart transplantation.

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